Effectiveness of a cognitive behavioural intervention for patients with undifferentiated somatoform disorder: results from the CIPRUS cluster randomized controlled trial in primary care

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Effectiveness of a cognitive behavioural intervention for patients with undifferentiated somatoform disorder: Results from the CIPRUS cluster randomized controlled trial in primary care

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ABSTRACT

Objective: To examine the effectiveness of a cognitive behavioural intervention delivered by mental health nurse practitioners (MHNPs) to patients with undifferentiated somatoform disorder (USD), compared to usual care.

Methods: We conducted a cluster randomized trial among primary care patients with USD comparing the intervention to usual care. The intervention consisted of six sessions with the MHNP. Primary outcome was physical functioning (RAND-36 physical component summary score). Secondary outcomes were the RAND-36 mental component summary score and the eight subscales; anxiety and depression (Hospital Anxiety and Depression Scale) and somatic symptom severity (Patient Health Questionnaire-15). Outcomes were assessed at baseline, 2, 4 and 12 months. We analysed data using linear mixed models by intention-to-treat, and investigated effect modifiers.

Results: Compared to usual care (*n*=87), the intervention group (*n*=111) showed an improvement in physical functioning (mean difference 2.24 [95% CI 0.51; 3.97]; *p*=.011), a decrease in limitations due to physical problems (mean difference 10.82 [95% CI 2.14; 19.49]; p.=0.015) and in pain (mean difference 5.08 [95% CI 0.58; 9.57]; *p*=.027), over 12 months. However effect sizes were small and less clinically relevant than expected. We found no differences for anxiety, depression and somatic symptom severity. Effects were larger and clinically relevant for patients with more recent symptoms and fewer physical diseases.

Conclusion: The cognitive behavioural intervention was effective in improving pain and physical functioning components of patients' health. It was particularly suitable for patients with symptoms that had been present for a limited number of years and with few comorbid physical diseases.

Trial registration: The trial is registered in the Dutch Trial Registry, www.trialregister.nl, under NTR4686.

INTRODUCTION

Medically unexplained physical symptoms (MUPS) are a diverse mixture of symptoms for which (currently) a medical explanation is lacking and which are extremely common in primary care (1,2). In a small percentage of patients with MUPS a specific disorder may eventually prove to be the cause of the symptoms (3). Although most MUPS are self-limiting, symptoms may persist and cluster. In the latter case symptoms may fulfil the diagnostic criteria for the DSM-IV undifferentiated somatoform disorder (USD) (4). If physical symptoms are accompanied by disproportionate emotional, cognitive and behavioural reactions, they may fulfil DSM-5 diagnostic criteria for somatic symptom disorder (5). These psychiatric disorders are associated with a large burden of disease, poor quality of life, functional impairment, depression and anxiety (6,7). Additionally, general practitioners (GPs) may experience some MUPS patients as 'difficult' or even 'heartsink' (8–10). They face a dilemma between pursuing medical investigations which will probably yield nothing important and may cause harm on the one hand, and refraining from further investigations with a very small chance of overlooking a (treatable) disease on the other hand (11,12). Patients may feel uncertain, confused and distressed upon hearing that their symptoms do not currently fit with a diagnosable illness, and may regard that message as implying that their symptoms are feigned or "all in the mind" (13,14). This may negatively impact their attitude towards mental health interventions for their symptoms.

Non-pharmacological interventions such as cognitive behavioural therapy (CBT) may improve functioning of patients with somatoform symptoms and reduce symptom severity (15). However, a German study found that only half of the patients with a somatoform disorder actually receive such mental health treatment (16), as CBT is commonly provided in secondary care or outside general practice. Patients and GPs may feel reluctant to turn to mental health services for physical symptoms. A CBT-based treatment provided in and suitable for primary care may therefore be a solution.

In the Dutch healthcare system, all citizens are registered with a general practice. The GP serves as gatekeeper to other healthcare providers. A recent reform of the Dutch mental healthcare system aimed to reduce the gap between general practice and mental health treatment (17). In 2014, the mental health nurse practitioner (MHNP) was introduced within general practice and currently nearly all surgeries in the Netherlands (87% in 2016) employ one (18). Dutch MHNPs have received higher vocational training in nursing or psychology and work under the supervision of the GP (17). They deliver short-term interventions to patients with psychosocial problems, but their expertise in psychological techniques such as CBT can vary.

The Dutch guideline on MUPS for GPs recommends that the MHNP offers treatment for MUPS when symptoms are mild to moderate (19). A standardized, evidence-based treatment could be helpful for patients and feasible for MHNPs to deliver. However, such an intervention has never been evaluated in this patient group. The main aim of this study was to examine the effectiveness of a new short-term CBT-based intervention delivered by MHNPs to patients with USD, as compared to usual care.

METHOD

Trial design

We performed a multicentre, cluster randomized controlled trial with two parallel groups comparing a CBT-based intervention on top of usual care, to usual care alone. The study design is described in more detail elsewhere (20).

We chose a cluster design in order to prevent contamination between patients in the same general practice and to prevent MHNPs from having to carry out the intervention with some of the patients and not carry it out with others, which might lead to contamination.

Ethics

The study was conducted according to the declaration of Helsinki (version 2013) and was approved by the VU University Medical Center Ethics Committee (number 2014.305, 9 July 2014 (amendment 5 August 2016).

Participants

Eligibility criteria

Participants were recruited from general practices across the Netherlands, were aged 18 years and above and met the DSM-IV criteria for USD. Exclusion criteria were: having a medical or psychological disorder that explained the symptoms; having a severe psychiatric disorder (e.g. psychotic disorder); currently receiving psychological help for USD; having poor language skills or physical handicaps interfering with understanding the intervention or questionnaires.

Inclusion procedure

GPs selected patients aged 18 years and above from their electronic database, who had consulted the GP with one or more symptoms from “Robbins' list” (21) at least twice in the previous 3 months. Robbins' list consists of 23 physical symptoms that are associated with functional somatic syndromes and can be found in the trial protocol (20). GPs checked the list of selected patients for exclusion criteria. Patients identified as potentially eligible received concise information about the study and the Patient Health Questionnaire 15-item somatic symptom severity scale (PHQ-15) (22) by mail from their GP. Patients with a PHQ-15 score of at least 5 (low symptom severity) and who were interested in participation in the study received extensive information. Patients were then invited to participate in a clinical interview (Structure Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (23)) to assess DSM-IV criteria for USD. Trained members of the research team administered these interviews by telephone. Patients meeting the criteria for USD received an informed consent form.

Intervention

The intervention consisted of six individual sessions of 30 min each with a MHNP. The intervention comprised a combination of two CBT-based techniques: a modified version of the ‘consequences model’ for somatoform disorders and Problem-Solving Treatment (PST). The consequences model is frequently used in treatment of somatoform disorders in Dutch secondary care (24,25). It focusses on the consequences or problems that arise due to somatoform complaints rather than on their causes, which are by definition unknown. The model assumes that physical symptoms may lead to various consequences in the patient's daily life, which are in fact survival strategies in reaction to the

physical symptoms. Although these survival strategies must have been beneficial initially (or they would not have been developed), they can aggravate symptoms and become harmful or devastating in the end. In the model, patients can improve their (physical) functioning and quality of life by strengthening the more beneficial, instead of the harmful, survival strategies in the end. Identified consequences or problems are then tackled using a CBT-based technique, which will be learned and applied by patients following the steps outlined in problem solving therapy (PST). PST is a practical treatment that is suitable for delivery by primary healthcare providers such as GPs and nurses (26,27). The goal was to support patients in developing survival strategies that are more helpful in the long run.

Each session was described in detail in the intervention manual that all MHNPs received during their training. In session 1 the MHNP introduced and explained the treatment, the patient told the MHNP about their physical symptoms and consequences/problems in his/her life due to these symptoms. A consequence/problem was defined as something the patient would like to achieve but is unable to at the moment. In session 2 the MHNP explained the PST goals and steps. In each of the sessions 3 through 6, the patient addressed a single consequence/problem, using the PST steps together with the MHNP. The goal was to stimulate people to practise improving their long-term problem solving skills, and to apply them to the consequences of their physical symptoms, but also to other problems in daily life. Patients applied the steps at home following written instructions. If not all the steps were covered during one session, they were addressed during the next session.

MHNPs

MHNPs followed two group training sessions lasting 3–3.5 h each. The training sessions were led by a clinical psychologist specialized in management of somatoform disorders. The training consisted of a theoretical part on USD, the consequences model and treatment rationale, and a practical part, in which MHNPs practiced PST. The clinical psychologist supervised the MHNPs during the study period.

Usual care

The usual care group did not receive any additional care, other than the usual care they received from their GP and any other healthcare providers they were referred to.

Outcome measures

Primary and secondary outcomes were assessed at baseline and 2, 4 and 12 months later. The measurements at 2 and 4 months corresponded to the intervention group being halfway through the intervention (3 sessions completed) and completing the intervention (6 sessions completed), respectively. Potential mediating variables were assessed at baseline and 2 and 4 months later. All outcome measures were assessed at the individual patient level.

Primary outcome

The primary outcome was the improvement in physical functioning during the total follow-up period, as measured by the physical component summary score (PCS) of the RAND-36 questionnaire. The PCS is one of the aggregated scores of the RAND-36, a validated questionnaire measuring health related quality of life. The raw scores were transformed into scores ranging from 0 to 100 with a higher score indicating better physical functioning (28). Item examples are “Does your health now

limit you in lifting or carrying groceries? If so, how much?" and "How much bodily pain have you had during the past 4 weeks?"

Secondary outcomes

Secondary outcomes were the mental component summary score (MCS) and the eight subscales of the RAND-36 (physical functioning, role limitations due to physical health problems, role limitations due to emotional problems, social functioning, emotional well-being, energy/ fatigue, bodily pain and general health perceptions). The scores of each separate subscale range from 0 to 100, higher scores indicating better health.

Depression and anxiety symptoms were measured by the Hospital Anxiety and Depression Scale (HADS) (29). This is an instrument with anxiety and depression subscales (HADS-A and HADS-D, respectively) with scores ranging from 0 to 21 for each scale. Higher scores indicate more severe symptoms. Somatization was measured with the PHQ-15 (22). This instrument has a score range of 0–30, with higher scores indicating higher somatic symptom severity.

Mediators

We took the following potential mediators into account: problem-solving skills (Social Problem-Solving Inventory) (30), health anxiety (Whitely Index) (31), cognitive and emotional representations of illness (brief version of the Illness Perception Questionnaire) (32), cognitive and behavioural responses to illness (Cognitive and Behavioural Responses Questionnaire) (33, 34), and level of perceived control (Pearlin Master Scale) (35). Data on these variables were collected at baseline, and at 2 and 4 months follow-up.

In the intervention group, we assessed the strength of the therapeutic alliance with the revised short-form Working Alliance Inventory (WAI-SR)) (36), at 2 months and at 4 months.

Process evaluation of the intervention

In order to better interpret our quantitative findings, we conducted a process evaluation by interviewing MHNPs from the intervention group. When they had completed most sessions, all 15 MHNPs were invited to participate in face-to-face interviews to evaluate their involvement in the trial; 13 accepted the invitation. The semi-structured interviews were based on a topic list with pre-identified themes.

At 4 months after baseline, patients in the intervention group were asked to answer 13 Likert items, evaluating their participation in the trial. The collected data were systematically analysed with both qualitative (interviews) and quantitative (questionnaire) methods.

Sample size

We aimed to detect a clinically relevant effect size of 0.4 sd on our primary outcome. We chose a two-sided significance level of 5% and a power of 80%. The allocation ratio was 1:1. We assumed a correlation coefficient of 0.5 for repeated measurements. Using linear mixed models with these values required a sample size of 74 patients per condition. We corrected for the cluster design with an expected average cluster size of 4 and assuming an ICC of 0.05 (37). Taking a potential dropout rate of 20% into account, we aimed to include 106 patients in each condition.

Randomization and blinding

At randomization, a cluster consisted of all participating general practices that employed one MHNP. An independent epidemiologist carried out concealed random allocation and assignment of clusters to the intervention group or control group by using a computer generated randomization list. She was not involved in the selection of general practices. In order to balance the size of the intervention and control groups, randomization was stratified according to cluster size (small: <5000 patients, and large: ≥5000 patients). Due to the nature of the intervention, it was not possible to blind researchers, GPs or patients to the allocation. MHNPs and GPs were informed about their allocation after signing a form that they agreed to participate. Patients were informed about their treatment allocation after they signed and returned the informed consent form.

Statistical analyses

We used descriptive statistics for baseline characteristics. The effect of the intervention on primary and secondary outcomes was analysed according to the intention-to-treat (ITT) principle (38). Linear mixed models analyses were used to take into account the dependence of repeated measurements in individual patients, without imputing missing data (39). Respondents were included if they had completed at least one follow-up measurement. For each outcome variable, we estimated the overall effect over time, and the effect per time point (2, 4 and 12 months after baseline). Time and the interaction between study group (intervention or control) and time were added to the models.

For each outcome measure, we performed a crude and adjusted analysis over the total follow-up period of 12 months. The crude analysis was only adjusted for the baseline value of the particular outcome. In the adjusted analysis, we evaluated whether the following variables were actual confounders: gender, age, level of education, duration of symptoms, somatic symptom severity (PHQ-15), anxiety symptoms (HADS-A), depressive symptoms (HADS-D), number of comorbid diseases, time intervals between completing baseline questionnaire and 2-month follow-up, and between completing the 2-month and 4-month follow-up questionnaires. We adjusted for the latter two because these intervals were different between the intervention group and the usual care group, for logistic reasons. Variables found to be actual confounders were added to the adjusted model.

For secondary outcomes, *p*-values should be interpreted cautiously due to multiple statistical comparisons, unless highly significant (e.g. $p < .01$).

To evaluate whether we should adjust for clustering within general practice, this variable was added as an additional level to the linear mixed model analysis. As this did not improve the model (likelihood ratio test: p=-0.90; ICC<0.01), clusters were not included in the final analyses.

All analyses were repeated applying the per protocol principle to the intervention group, as exploratory analyses. We defined three different per protocol populations: intervention patients who had 1) attended all 6 sessions with their MHNP (n=57); 2) attended all 6 sessions or less if their goals were achieved earlier (n=62); 3) attended at least 4 sessions (n=76). All control group patients were included in the per protocol analysis (n=87).

We carried out additional analyses by adding interaction terms to evaluate whether any of the pre-determined variables (age, gender, education level, symptom duration, somatic symptom severity

(PHQ-15), physical comorbidity and anxiety and depressive symptoms (HADS)) were effect modifiers. These variables were chosen based on the Dutch multidisciplinary guideline for the management of MUPS and somatoform disorders, which identifies them as relevant factors in discerning patient profiles (40). Mediation analyses were carried out based on Krull & MacKinnon (41), using the Sobel-Goodman test to determine significance. The relationship between primary outcome and working alliance was assessed using Pearson's r.

Cohen's d for measuring effect size was calculated by dividing the regression coefficient of each outcome by its standard deviation. We used standard deviations for the total group at baseline.

Data were analysed using IBM SPSS Statistics version 22 and Stata version 14.

RESULTS

Recruitment

Recruitment of patients took place between August 2015 and March2017. Recruitment stopped when a total of 213 informed consent forms had been returned. Figure 1 provides an overview of the enrolment procedure.

Baseline characteristics

Socio-demographic and clinical baseline characteristics of the participants are provided in Table 1. The mean age of the total sample was 51.5 years (sd=16.3) and the majority of patients (74.5%) were female. There were more female patients (79.8%) in the control group than in the intervention group (70.3%) and the level of completed education was lower. The median duration of symptoms in the total sample was 5.7 years (IQR=2.7–15.7) and most commonly reported were musculoskeletal complaints (72.0%). Neurological symptoms were more common in the intervention group (35.1%) than in the control group (18.0%).

Numbers analysed

Data on the primary outcome on at least one follow-up assessment were available for 97/111 (87.4%) patients in the intervention group and 75/87 (86.2%) patients in the control group. Figure 1 provides more details on withdrawals.

Primary outcome

Fig. 2 visually represents the course of the RAND-36 PCS for both groups. The ITT analysis showed a significant intervention effect over the 12 month period on patients' physical functioning (PCS score difference 2.24 [95% CI 0.51; 3.97]; *p*=.011; Cohen's d=0.23) (Table 2). Results per time point are presented in Appendix A. There was a statistically significant difference at 4 months after baseline (PCS score difference 2.93 [95% CI 0.77; 5.09]; *p*=.008; Cohen's d=0.30).

Secondary outcomes

Significant intervention effects over 12 months were also found on patients' limitations in functioning due to physical health problems (RAND-36 role functioning/physical score difference 10.82 [95% CI 2.14; 19.49]; p.=0.015; Cohen's d=0.33) and bodily pain (RAND-36 bodily pain score difference 5.08 [95% CI 0.58; 9.57]; *p*=.027; Cohen's d=0.23) (Table 2).

When investigating the effects per time point (Appendix A), the largest and statistically significant differences were found at 4 months after baseline. Although there was no overall effect on the RAND-36 physical functioning subscale, there was a significant difference at 4 months (5.00 points [95% CI 0.28; 9.73]; *p*=.038; Cohen's d=0.20).

No significant intervention effects were found for the remaining domains of health related quality of life, anxiety, depression and somatic symptom severity.

Effect modification

Reported duration of symptoms at baseline significantly modified the effect of our intervention on the RAND-36 PCS (p=0.011), bodily pain (p=0.048) and general health subscales (p=0.006). Physical comorbidity significantly modified the intervention effect on the RAND-36 PCS (p=0.026) and general health subscale (p=0.031). No other variable modified any of the effects. In order to report the results separately, we split each effect-modifying variable on its median. Table 3 summarizes the results per group and Appendix B provides results per time point.

Generally, patients with a shorter duration of symptoms and fewer comorbid physical diseases showed improvement, as opposed to those with a longer duration of symptoms, who reported poorer general health after the intervention.

Mediation

None of the potential mediators actually mediated the effect on the primary outcome. With regard to the working alliance between patient and MHNP in the intervention group, a weak, but significant, positive correlation was found between the RAND-36 PCS change score between baseline and 4 months and the WAI-SR bond scale (r=0.258, n=78, p=0.022) at 4 months after baseline.

Exploratory analyses

The results of the per protocol analyses are provided in Appendices C, D and E. For nearly all outcome variables the effect was similar to those in the ITT analyses.

Evaluation by MHNPs and patients

MHNPs were satisfied with the amount and content of training they received before delivering the intervention. Most found that 30 min was not enough for a single session. They reported that they generally adhered to the protocol but sometimes adjusted the length and pace of sessions by taking more time. MHNPs considered the CBT-based intervention to be a suitable technique for treating USD, that enhanced patients' problem-solving abilities and activated them in their daily life. MHNPs felt that most patients benefited from the intervention, as their functioning became less impaired, but thought that the intervention might not be effective for patients with comorbid physical and psychological disorders, psychosocial problems or a lower IQ.

Most MHNPs would use (elements of) the protocol again in the future. Those who would use the protocol again said the treatment manual improved their proficiency in a CBT-based intervention, provided them with structure during sessions and a more problem-solving mindset. For future use, MHNPs recommended personalizing the number and pace of sessions to the patient, and offering

other treatment methods alongside the CBT-based method, such as Acceptance and Commitment Therapy, psychoeducation, and physical activation.

86 patients (77%) completed the patient evaluation questionnaire at 4 months after baseline. The (selected) results are provided in Table 4. The majority of patients (66%) rated the quality of the intervention as good, 11% as excellent, 14% as mediocre and 1 person (1%) as very poor. Half of the patients (51%) reported that the intervention helped them deal with their physical symptoms, 22% were neutral and 17% said it did not help. Most patients were fairly (42%), or extremely satisfied (25%) with the intervention and 20% were neutral. Only a few were (somewhat) unsatisfied (4%). More than half (54%) said they would certainly or probably recommend the intervention to a friend or family member with USD.[1]

DISCUSSION

Summary of findings

Our intervention improved physical components of patients' health. Physical functioning improved, bodily pain and limitations due to physical problems and pain decreased. This effect was more pronounced for patients with physical symptoms that had been present for a limited number of years and with few comorbid physical diseases. These patients also experienced improved general health.

Our study demonstrates that a relatively short and light intervention such as ours in primary care is suitable for patients with less persistent symptoms, but insufficient for those with more persistent symptoms. Our findings are supported by information from the interviews with the MHNPs, most of whom clearly distinguished between more severe an less severe patients, and reported that the latter benefited more from the intervention. Patients with symptoms that had lasted longer than the median duration deteriorated somewhat in their general health perceptions after our intervention. These patients assessed their health as poor and expected it to deteriorate further in the future. A possible explanation is that these patients, whose symptoms are already more difficult to treat due to their duration, became demoralized after receiving (possibly yet another) treatment that did not seem to help. In general, patients in the intervention group were satisfied with the intervention. Although most patients reported that they were satisfied with the intervention and would recommend it to a friend with MUPS, a smaller percentage was less positive. Presumably these were the intervention.

Surprisingly, none of the variables that we hypothesized to be potential mediators actually mediated the effect on patients' well-being and symptoms. Thus, our study was unable to shed light on the mechanism of change. We did find a positive, though low, correlation with therapeutic alliance, which corresponds to previous findings of a positive therapeutic relationship being partly responsible for the effects of a psychological intervention and improving quality of life (42,43).

Embedding in existing literature

Overall we found statistically significant effects of our intervention, but effect sizes were small (d=0.22 for RAND-36 PCS, d=0.33 for role functioning/physical, and d=0.23 for bodily pain), and lower than we aimed for (0.4 sd for the RAND-36 PCS). Also, the effect on the primary outcome was not

[1] Figures in this paragraph do not add to 100% due to missing values.

clinically relevant (difference of 2.24 whereas a difference of 3–5 is considered clinically relevant (44)). However, effect sizes for the primary outcome were substantially higher in patients with a duration of symptoms shorter than the median (0.39) and with < 3 comorbid physical diseases (0.36). These are considered small, clinically relevant effect sizes. Our overall results are in line with previous findings from RCTs that investigated psychological interventions for patients with somatic complaints (15), where small to medium effect sizes are usually found on functional disability and quality of life. The effect sizes in our trial are also of similar magnitude to those demonstrated for interventions administered in primary care for other common mental disorders such as depression and anxiety (45,46). For patients who do not respond to brief primary care based interventions, more intense interventions could be offered (47,48).

In previous research the effectiveness of psychological interventions for patients with multiple MUPS was investigated when provided by various healthcare providers, such as psychotherapists and GPs (49). We investigated the effectiveness of an intervention carried out by MHNPs, a new role in Dutch primary care. Interventions by nurse practitioners seem to have beneficial effects on patient satisfaction and quality of life in primary care patients with somatic problems (50). On the flip side, a recent study in Dutch general practices found that having a MHNP in the surgery resulted in MHNPs offering additional long consultations to patients with mental health problems, but did not reduce visits to the GP (17). Interventions delivered by MHNPs in general and for patients with somatoform complaints in particular must, therefore, be studied more extensively. Furthermore, incorporating other treatment methods such as physical exercise (49) or relaxation and mindfulness techniques (51) could be helpful for this patient group.

Strengths and limitations

This is the first study that examined the effects of an individual, CBT-based intervention by MHNPs for patients with USD versus usual care. We conducted the study in the actual setting of the general practice, making this treatment easier to implement. Another strength of this study is that we used qualitative data from process evaluation interviews with the MHNPs to deepen understanding of our results.

Although the desired number of patients signed an informed consent form (*n*=213), not all of them completed all of the measurements. The dropout rate also turned out higher than expected (27% rather than 20%). This might be attributed to our case-finding (persons might be less motivated to change), a relatively long follow-up period (12 months) and the length of the questionnaires.

Furthermore, we used the diagnosis of USD according to the, now outdated, DSM-IV, as our trial was initiated in the transition period from DSM-IV to DSM-5, and a diagnostic interview for the DSM-5 was not available yet. The entire DSM-IV category ‘somatoform disorders’, to which USD belonged (4), has been replaced by ‘somatic symptom disorder’ (SSD) in the DSM-5 (5). A study comparing these diagnostic criteria found that patients with SSD always fulfil the criteria for USD, and have more severe symptoms and a lower quality of life (52). Therefore, as all SSD patients fulfil the criteria for USD, our findings could be generalizable to patients with SSD. However, considering that the latter are a more severe group and as our findings show that patients with a longer duration of symptoms do not benefit from our intervention, this needs to be verified in future studies.

We opted for cluster randomization, in order to keep the effect of the intervention as pure as possible, so that trained MHNPs would not have to switch between providing and not providing the intervention to similar patients. However, the choice to use cluster randomization also implied using larger clusters and a more complex definition of cluster because individual various MHNPs working in the same surgery also worked part-time in separate other surgeries.

A final point of consideration is that our trial was conducted in the Dutch healthcare setting, in which every citizen has access to general practice and virtually every general practice has an employed MHNP. Our results may be less generalizable to countries with different healthcare systems.

CONCLUSION

Our study demonstrated promising results for a nurse-led CBT-based intervention for patients with USD over usual primary care. The short-term and relatively light intervention appears effective for patients with a shorter symptom duration and with few other somatic diseases.

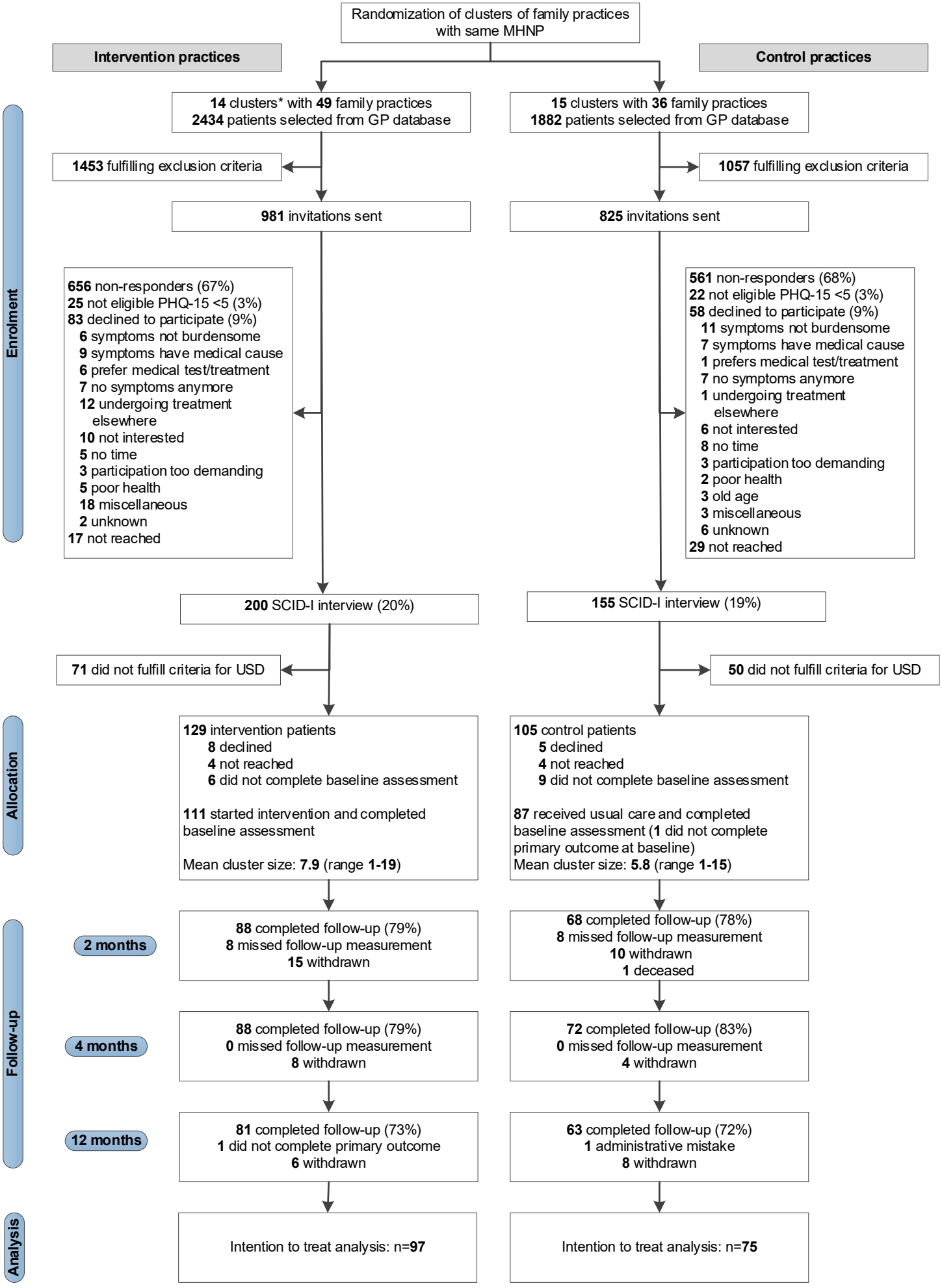
Randomization of clusters of family practices with same MHNP
Intervention practices
Control practices
Enrolment
14 clusters* with 49 family practices
2434 patients selected from GP database
15 clusters with 36 family practices
1882 patients selected from GP database
1453 fulfilling exclusion criteria
1057 fulfilling exclusion criteria
981 invitations sent
825 invitations sent
656 non-responders (67%)
25 not eligible PHQ-15 <5 (3%)
83 declined to participate (9%)
6 symptoms not burdensome
9 symptoms have medical cause
6 prefer medical test/treatment
7 no symptoms anymore
12 undergoing treatment elsewhere
10 not interested
5 no time
3 participation too demanding
5 poor health
18 miscellaneous
2 unknown
17 not reached
561 non-responders (68%)
22 not eligible PHQ-15 <5 (3%)
58 declined to participate (9%)
11 symptoms not burdensome
7 symptoms have medical cause
1 prefers medical test/treatment
7 no symptoms anymore
1 undergoing treatment elsewhere
6 not interested
8 no time
3 participation too demanding
2 poor health
3 old age
3 miscellaneous
6 unknown
29 not reached
200 SCID-I interview (20%)
155 SCID-I interview (19%)
71 did not fulfill criteria for USD
50 did not fulfill criteria for USD
Allocation
129 intervention patients
8 declined
4 not reached
6 did not complete baseline assessment
111 started intervention and completed baseline assessment
Mean cluster size: 7.9 (range 1-19)
105 control patients
5 declined
4 not reached
9 did not complete baseline assessment
87 received usual care and completed baseline assessment (1 did not complete primary outcome at baseline)
Mean cluster size: 5.8 (range 1-15)
Follow-up
2 months
88 completed follow-up (79%)
8 missed follow-up measurement
15 withdrawn
68 completed follow-up (78%)
8 missed follow-up measurement
10 withdrawn
1 deceased
4 months
88 completed follow-up (79%)
0 missed follow-up measurement
8 withdrawn
72 completed follow-up (83%)
0 missed follow-up measurement
4 withdrawn
12 months
81 completed follow-up (73%)
1 did not complete primary outcome
6 withdrawn
63 completed follow-up (72%)
1 administrative mistake
8 withdrawn
Analysis
Intention to treat analysis: n=97
Intention to treat analysis: n=75

Figure 1. Flow of study participants

* For the intervention group, a cluster was composed by matching MHNPs to all participating general practices where the MHNP works and to all other MHNPs who also worked in these general practices.

GP General practitioner; *MHNP* mental health nurse practitioner; *PHQ-15* Patient Health Questionnaire 15-item somatic symptom severity scale; *SCID-I* Structured Clinical Interview for DSM-IV Axis I Disorders

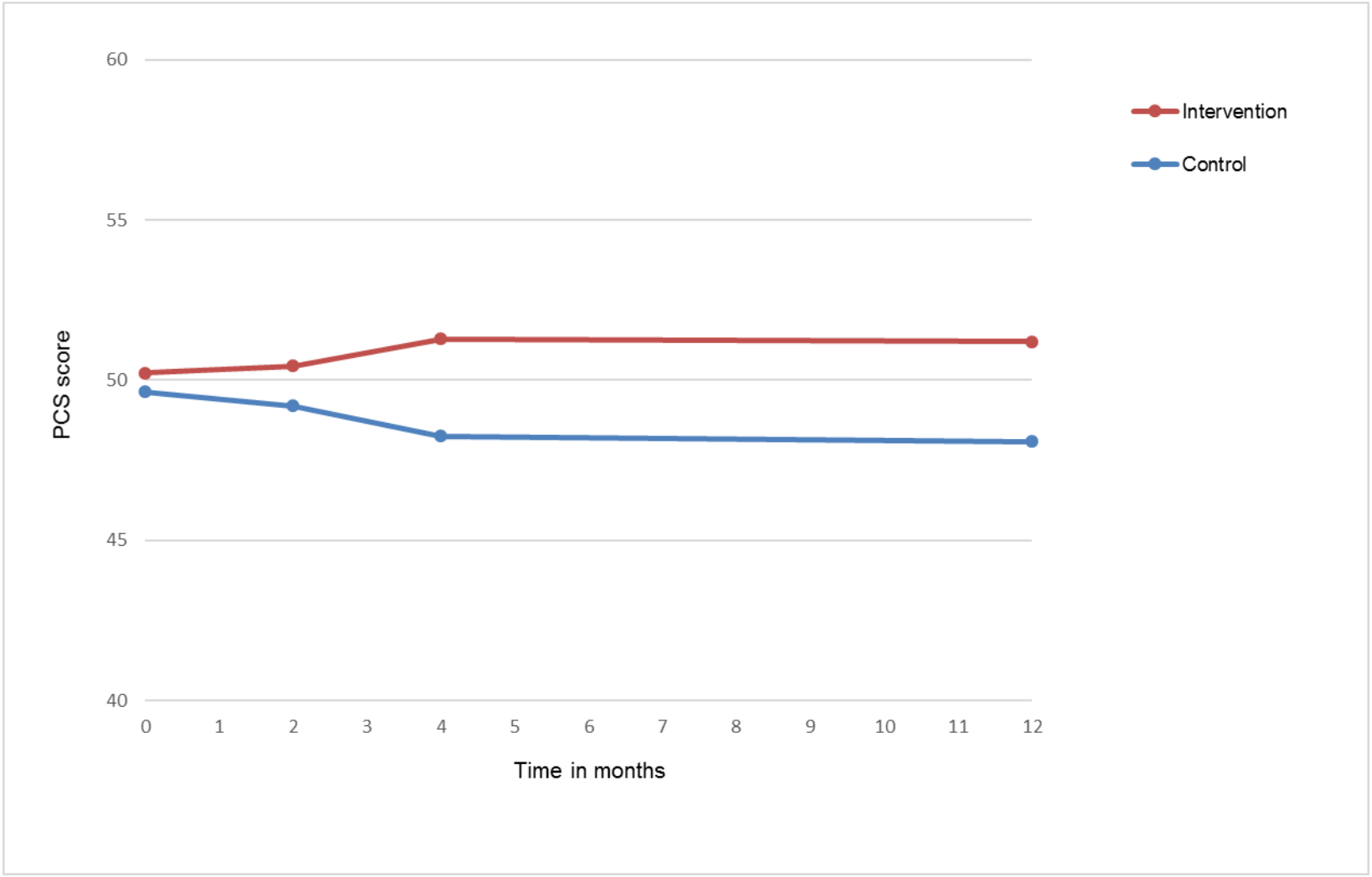

Figure 2. 12-month course of physical functioning as measured with the RAND-36 Physical Component Summary score (PCS)

Table 1. Patients' baseline characteristics			
Characteristics	**Intervention group (n=111)**	**Control group (n=89)** [a]	**Total sample (n=200)** [b]
Age, mean (sd)	53.00 (15.47)	49.69 (17.13)	51.53 (16.3)
Female	78 (70.3%)	71 (79.8%)	149 (74.5%)
Both parents born in the Netherlands	90 (81.1%)	72 (80.9%)	162 (81.0%)
Educational level			
Low	8 (7.3%)	7 (8.0%)	15 (7.6%)
Medium	58 (52.3%)	54 (62.1%)	112 (56.9%)
High education	44 (40.0%)	26 (29.8%)	70 (35.5%)
Work status [c]			
Employed	43 (38.7%)	36 (40.4.%)	79 (39.5%)
Unemployed	68 (61.3%)	53 (59.6%)	121 (60.5%)
Living situation			
Alone	28 (25.2%)	23 (25.8%)	51 (25.5%)
Not alone	83 (74.8%)	66 (74.2%)	149 (74.5%)
Symptom duration in years (self-report), median (IQR)	5.2 (2.8-15.5)	6.1 (2.7-16.1)	5.7 (2.7-15.7)
Most prominent symptoms [c]			
Musculoskeletal	78 (70.3%)	66 (74.2%)	144 (72.0%)

General and unspecified	41 (36.9%)	36 (40.4%)	77 (38.5%)
Neurological	39 (35.1%)	16 (18.0%)	55 (27.5%)
Psychological	19 (17.1%)	18 (20.2%)	37 (18.5%)
Digestive	11 (9.9%)	7 (7.9%)	18 (9.0%)
Number of comorbid physical diseases, mean (sd)	3.16 (2.50)	3.34 (2.41)	3.24 (2.46)
Most reported comorbid physical diseases [c]			
Back problems	79 (71.2%)	63 (70.8%)	142 (71.0%)
Pulmonary	40 (36.0%)	28 (31.5%)	68 (34.0%)
Neurological	35 (31.5%)	31 (34.8%)	66 (33.0%)
Number of self-report comorbid psychiatric disorders, mean (sd)	0.69 (0.91)	0.71 (1.19)	0.70 (1.04)
Most reported comorbid psychiatric disorders [c]			
Distress/burn-out	27 (24.5%)	18 (20.9%)	45 (23.0%)
Depression	26 (23.4%)	17 (19.5%)	43 (21.7%)
Anxiety	19 (17.1%)	16 (17.4%)	34 (17.3%)
RAND-36			
PCS (primary outcome)	50.22 (9.89)	49.64 (9.81)	49.97 (9.83)
MCS	49.80 (9.97)	50.22 (10.93)	49.99 (10.38)
Physical functioning	62.78 (25.08)	59.25 (26.12)	61.23 (25.54)

Role functioning/physical	21.62 (32.59)	25.29 (32.84)	23.21 (32.67)
Role functioning/emotional	56.52 (44.13)	52.61 (46.01)	54.84 (44.87)
Social functioning	55.63 (27.73)	57.76 (27.84)	56.57 (27.73)
Bodily pain	46.24 (21.31)	45.79 (22.19)	46.04 (21.64)
Emotional well-being	59.72 (17.04)	60.43 (20.23)	60.03 (18.43)
Energy/fatigue	36.89 (16.90)	38.65 (15.95)	37.65 (16.48)
General health	43.81 (17.64)	41.43 (16.25)	42.78 (17.05)
Anxiety (HADS-A)	7.89 (3.80)	7.69 (4.52)	7.80 (4.11)
Depression (HADS-D)	7.00 (3.86)	7.52 (4.23)	7.22 (4.02)
Somatic symptom severity (PHQ-15)	13.63 (4.89)	13.47 (4.43)	13.56 (4.69)

Results are expressed as *n* (%) unless stated otherwise, and in *mean (sd)* for the RAND-36, HADS and PHQ-15.
Abbreviations: HADS: Hospital Anxiety and Depression Scale; MCS: Mental Component Summary Score; MUS: medically unexplained symptoms; PCS: Physical Component Summary Score; PHQ-15: Patient Health Questionnaire 15-item somatic symptom severity scale; sd: standard deviation

[a] 89 patients completed items on demographic characteristics, but 87 patients completed the primary outcome. Therefore, due to missing values, the available *n* ranged from 87-89.
[b] Due to missing values the available *n* ranged from 188-200.
[c] More than one answer option was permitted, so numbers do not necessarily add up to 100%

Table 2. Results of the mixed models Intention-To-Treat analyses

	Crude analyses		Adjusted analyses [a]	
	B (95% CI)	**p-value**	**B (95% CI)**	**p-value**
Primary outcome				
RAND-36 Physical component summary score (PCS)	1.80 (0.19 to 3.42)	0.029*	2.24 (0.51 to 3.97)	0.011*
Secondary outcomes				
RAND-36				
Mental component summary score (MCS)	-0.55 (-2.47 to 1.37)	0.57	-0.35 (-2.22 to 1.52)	0.71
Physical functioning	1.47 (-2.08 to 5.02)	0.42	2.33 (-1.40 to 6.06)	0.21
Role functioning/physical	7.17 (-1.16 to 15.50)	0.091	10.82 (2.14 to 19.49)	0.015*
Role functioning/emotional	-2.14 (-11.63 to 7.36)	0.66	1.41 (-8.29 to 11.10)	0.78
Social functioning	2.65 (-2.85 to 8.14)	0.35	2.66 (-3.09 to 8.41)	0.37
Bodily pain	3.98 (-0.31 to 8.27)	0.069	5.08 (0.58 to 9.57)	0.027*
Emotional well-being	-0.77 (-3.88 to 2.35)	0.63	-0.13 (-3.28 to 3.02)	0.93
Energy/fatigue	2.56 (-0.64 to 5.75)	0.12	1.98 (-1.24 to 5.20)	0.23
General health	-0.28 (-3.90 to 3.34)	0.88	0.05 (-3.91 to 4.02)	0.98
Anxiety symptoms (HADS-A)	0.30 (-0.33 to 0.94)	0.35	0.33 (-0.29 to 0.94)	0.30
Depressive symptoms (HADS-D)	-0.06 (-0.66 to 0.55)	0.86	-0.23 (-0.89 to 0.43)	0.49
Somatic symptom severity (PHQ-15)	-0.51 (-1.43 to 0.40)	0.27	-0.69 (-1.64 to 0.24)	0.15

Abbreviations: 95%CI: 95% Confidence Interval; HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale; MCS: Mental Component Summary Score; PCS: Physical Component Summary Score; PHQ-15: Patient Health Questionnaire 15-item somatic symptom severity scale

a: adjusted for (if necessary): gender, age, level of education, duration of symptoms, somatic symptom severity (PHQ-15), anxiety symptoms (HADS-A), depressive symptoms (HADS-D), number of comorbid physical diseases, time interval baseline – 2-months follow-up, time interval baseline – 4-months follow-up

* $p<0.05$

Table 3. Results of crude mixed models analyses per group for symptom duration and physical comorbidity

	Symptom duration below median (n=70-98)		**Symptom duration above median (n=72-98)**	
	Overall difference B (95% CI)	**p-value**	**Overall difference B (95% CI)**	**p-value**
Primary outcome RAND-36 PCS	3.83 (1.57 to 6.09)	0.001*	-0.18 (-2.40 to 2.03)	0.87
Secondary outcomes RAND-36				
Bodily pain	6.94 (1.05 to 12.84)	0.021*	0.68 (-5.41 to 6.78)	0.83
General health	5.74 (0.96 to 10.52)	0.019*	-5.98 (-11.09 to -0.86)	0.022*

	0-2 comorbid physical diseases (n=69-91)		**3 or more comorbid physical diseases (n=75-106)**	
	Overall difference B (95% CI)	**p-value**	**Overall difference B (95% CI)**	**p-value**
Primary outcome RAND-36 PCS	3.55 (1.13 to 5.97)	0.004*	-0.02 (-2.09 to 2.05)	0.99
Secondary outcome RAND-36 General health	2.38 (-2.60 to 7.36)	0.35	-3.09 (-8.16 to 1.98)	0.23

Abbreviations: 95%CI: 95% Confidence Interval; PCS: Physical Component Summary Score

* $p<0.05$

Table 4. (Selected) results from the patient evaluation questionnaire*

1. Did the individual training help you deal better with your physical complaints?	*Yes, it helped me a lot*	*Yes, it helped me somewhat*	*Neutral*	*No, it did not help me*	*No, it aggravated my complaints*
	4.6%	46.0%	21.8%	17.2%	0%
2. What did you think of the quality of the individual training that you followed?	*Excellent*	*Good*	*Medium*	*Bad*	*Very bad*
	10.3%	65.5%	13.8%	0%	1.1%
3. Did the intervention meet your expectations?	*All my expectations were met*	*Most of my expectations were met*	*Some of my expectations were met*	*Only a few of my expectations were met*	*None of my expectations were met*
	8.0%	35.6%	21.8%	18.4%	5.7%
4. How satisfied are you in general with the intervention you received?	*Very satisfied*	*Somewhat satisfied*	*Neutral*	*Somewhat unsatisfied*	*Very unsatisfied*
	25.3%	41.4%	19.5%	3.4%	1.1%

5. Imagine that someone you know happens to have unexplained physical complaints, would you recommend this intervention?	*Yes, definitely*	*Yes, I think so*	*Maybe*	*No, I don't think so*	*No, definitely not*
	23.0%	31.0%	26.4%	11.5%	0%
6. Imagine that you encounter unexplained physical symptoms again in the future, would you follow this intervention again with your MHNP?	*Yes, definitely*	*Yes, I think so*	*Maybe*	*No, I don't think so*	*No, definitely not*
	17.2%	14.9%	28.7%	26.4%	3.4%

* Numbers do not add up to 100% due to missing values

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Appendix A. Detailed results of the mixed models ITT analyses

Primary outcome **RAND-36 PCS**	**Intervention group** **(mean, sd)**	**Control group** **(mean, sd)**	**Crude analyses**		**Adjusted analyses** [a]	
Baseline	50.22 (9.89)	49.64 (9.81)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	50.45 (9.67)	49.18 (9.01)	1.25 (-0.81 to 3.30)	0.24	1.66 (-0.52 to 3.84)	0.14
4 months	51.28 (10.57)	48.23 (8.77)	2.08 (0.05 to 4.12)	0.045*	2.93 (0.77 to 5.09)	0.008*
12 months	51.21 (9.93)	48.09 (10.53)	2.10 (-0.02 to 4.23)	0.053	2.09 (-0.14 to 4.33)	0.066
Overall effect	n/a	n/a	1.80 (0.19 to 3.42)	0.029*	2.24 (0.51 to 3.97)	0.011*
Secondary outcomes **RAND-36 MCS**	**Intervention group** **(mean, sd)**	**Control group** **(mean, sd)**	**Crude analyses**		**Adjusted analyses** [a]	
Baseline	49.80 (9.97)	50.22 (10.93)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**

2 months	50.05 (10.13)	50.12 (10.28)	-0.02 (-2.46 to 2.43)	0.99	0.02 (-2.37 to 2.42)	0.99
4 months	49.67 (10.09)	50.25 (10.26)	-0.69 (-3.10 to 1.73)	0.58	-0.67 (-3.10 to 1.76)	0.59
12 months	49.68 (9.22)	50.44 (10.51)	-1.02 (-3.54 to 1.51)	0.43	-0.44 (-2.97 to 2.08)	0.73
Overall effect	n/a	n/a	-0.55 (-2.47 to 1.37)	0.57	-0.35 (-2.22 to 1.52)	0.71
RAND-36 Physical functioning	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses [a]**	
Baseline	62.78 (25.08)	59.25 (26.12)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	61.68 (25.81)	57.79 (25.44)	0.04 (-4.48 to 4.57)	0.99	0.56 (-4.16 to 5.28)	0.82
4 months	66.42 (25.36)	58.71 (26.70)	3.66 (-0.84 to 8.16)	0.11	5.00 (0.28 to 9.73)	0.038*
12 months	67.77 (23.61)	60.63 (28.98)	0.65 (-4.05 to 5.35)	0.79	1.35 (-3.63 to 6.13)	0.62
Overall effect	n/a	n/a	1.47 (-2.08 to 5.02)	0.42	2.33 (-1.40 to 6.06)	0.21
RAND-36 Role functioning/physical	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses [a]**	
Baseline	21.62 (32.59)	25.29 (32.84)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	28.45 (36.00)	29.96 (35.71)	3.56 (-7.43 to 14.56)	0.53	7.18 (-4.33 to 18.69)	0.22

4 months	35.51 (41.47)	27.38 (34.20)	9.33 (-1.54 to 20.20)	0.093	13.57 (2.21 to 24.92)	0.019*
12 months	38.75 (41.13)	30.24 (38.18)	8.77 (-2.65 to 20.20)	0.13	11.51 (-0.35 to 23.37)	0.057
Overall effect	n/a	n/a	7.17 (-1.16 to 15.50)	0.091	10.82 (2.14 to 19.49)	0.015*
RAND-36 Role functioning/emotional	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses** [a]	
Baseline	56.52 (44.13)	52.61 (46.01)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	58.24 (44.96)	57.21 (44.12)	-3.21 (16.19 to 9.77)	0.63	0.03 (-13.26 to 13.31)	1.00
4 months	58.62 (43.42)	58.10 (45.64)	-2.45 (-15.26 to 10.36)	0.71	0.66 (-12.47 to 13.78)	0.92
12 months	62.71 (43.76)	60.22 (45.10)	-0.62 (-14.10 to 12.86)	0.93	3.55 (-10.21-17.31)	0.61
Overall effect	n/a	n/a	-2.14 (-11.63 to 7.36)	0.66	1.41 (-8.29 to 11.10)	0.78
RAND-36 Social functioning	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses** [a]	

Baseline	55.63 (27.73)	57.76 (27.84)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	64.49 (25.91)	62.87 (24.24)	2.44 (-4.54 to 9.41)	0.45	2.04 (-5.31 to 9.40)	0.59
4 months	64.77 (24.75)	63.19 (26.533)	1.85 (-5.05 to 8.75)	0.60	2.22 (-5.05 to 9.50)	0.55
12 months	67.59 (24.83)	63.10 (27.63)	3.78 (-3.42 to 10.98)	0.30	3.74 (-3.80 to 11.28)	0.33
Overall effect	n/a	n/a	2.65 (-2.85 to 8.14)	0.35	2.66 (-3.09 to 8.41)	0.37
RAND-36 Bodily pain	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses** [a]	
Baseline	46.24 (21.31)	45.79 (22.19)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	52.85 (21.71)	49.55 (24.01)	3.26 (-2.22 to 8.74)	0.24	4.45 (-1.24 to 10.14)	0.13
4 months	56.77 (21.42)	50.17 (21.77)	4.98 (-0.44 to 10.40)	0.072	6.45 (0.83 to 12.08)	0.025*
12 months	57.19 (20.20)	51.21 (25.89)	3.69 (-1.97 to 9.34)	0.20	4.08 (-1.75 to 9.91)	0.17
Overall effect	n/a	n/a	3.98 (-0.31 to 8.27)	0.069	5.08 (0.58 to 9.57)	0.027*
RAND-36 Emotional well-being	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses** [a]	
Baseline	59.72 (17.04)	60.43 (20.23)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**

2 months	60.18 (17.43)	60.50 (20.29)	0.04 (-3.91 to 4.00)	0.98	0.22 (-3.80 to 4.23)	0.92
4 months	63.91 (18.61)	63.77 (19.30)	-0.12 (-4.04 to 3.80)	0.95	0.85 (-3.14 to 4.85)	0.68
12 months	62.76 (16.84)	64.51 (19.81)	-2.36 (-6.43 to 1.71)	0.23	-1.68 (-5.79 to 2.44)	0.43
Overall effect	n/a	n/a	-0.77 (-3.88 to 2.35)	0.63	-0.13 (-3.28 to 3.02)	0.93
RAND-36 Energy/fatigue	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses [a]**	
Baseline	36.89 (16.90)	38.65 (15.95)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	40.19 (17.18)	38.80 (15.81)	3.31 (-0.87 to 7.49)	0.12	2.08 (-2.15 to 6.31)	0.34
4 months	42.82 (18.12)	41.36 (14.32)	2.22 (-1.91 to 6.36)	0.29	1.76 (-2.44 to 5.96)	0.41
12 months	46.71 (18.70)	46.06 (17.81)	2.05 (-2.25 to 6.36)	0.35	1.90 (-2.43 to 6.24)	0.39
Overall effect	n/a	n/a	2.56 (-0.64 to 5.75)	0.12	1.98 (-1.24 to 5.20)	0.23
RAND-36 General health	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses [a]**	
Baseline	43.81 (17.64)	41.43 (16.25)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	44.51 (17.86)	43.50 (16.67)	-0.60 (-3.82 to 5.02)	0.79	0.64 (-4.11 to 5.38)	0.79

4 months	47.14 (20.38)	47.54 (18.06)	-1.53 (-5.91 to 2.84)	0.49	-1.21 (-5.92 to 3.50)	0.62
12 months	49.09 (19.37)	47.06 (17.47)	0.28 (-4.23 to 4.79)	0.91	0.63 (-4.21 to 5.46)	0.80
Overall effect	n/a	n/a	-0.28 (-3.90 to 3.34)	0.88	0.05 (-3.91 to 4.02)	0.98
Anxiety symptoms (HADS-A)	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses [a]**	
Baseline	7.89 (3.80)	7.69 (4.52)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	8.47 (4.22)	7.32 (4.28)	0.48 (-0.34 to 1.29)	0.25	0.51 (-0.29 to 1.31)	0.21
4 months	7.46 (4.07)	6.72 (4.43)	0.19 (-0.62 to 1.00)	0.65	0.17 (-0.63 to 0.98)	0.67
12 months	6.89 (4.09)	6.26 (4.41)	0.24 (-0.60 to 1.08)	0.58	0.32 (-0.50 to 1.15)	0.44
Overall effect	n/a	n/a	0.30 (-0.33 to 0.94)	0.35	0.33 (-0.29 to 0.94)	0.30
Depressive symptoms (HADS-D)	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses [a]**	
Baseline	7.00 (3.86)	7.52 (4.23)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	6.93 (3.91)	7.26 (4.29)	-0.05 (-0.83 to 0.72)	0.89	-0.12 (-0.93 to 0.68)	0.77
4 months	6.29 (4.04)	6.62 (4.31)	-0.06 (-0.84 to 0.71)	0.87	-0.21 (-1.02 to 0.60)	0.61

12 months	5.83 (4.15)	6.29 (4.54)	-0.05 (-0.85 to 0.75)	0.90	-0.34 (-1.17 to 0.48)	0.42
Overall effect	n/a	n/a	-0.06 (-0.66 to 0.55)	0.86	-0.23 (-0.89 to 0.43)	0.49
Somatic symptom severity (PHQ-15)	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Crude analyses**		**Adjusted analyses** [a]	
Baseline	13.63 (4.89)	13.47 (4.43)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	13.13 (5.36)	13.74 (5.23)	-1.06 (-2.25 to 0.14)	0.083	-1.19 (-2.42 to 0.04)	0.057
4 months	12.83 (5.20)	12.74 (4.95	-0.05 (-1.25 to 1.14)	0.93	-0.33 (-1.56 to 0.91)	0.60
12 months	11.86 (5.27)	12.03 (5.78)	-0.04 (-1.62 to 0.89)	0.56	-0.47 (-1.75 to 0.80)	0.47
Overall effect	n/a	n/a	-0.51 (-1.43 to 0.40)	0.27	-0.69 (-1.64 to 0.24)	0.15

Abbreviations: 95%CI: 95% Confidence Interval; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; n/a: not applicable; ITT: Intention to Treat; MCS: Mental Component Summary Score; PCS: Physical Component Summary Score; PHQ-15: Patient Health Questionnaire 15-item somatic symptom severity scale; sd: standard deviation

[a] adjusted for (if necessary): gender, age, level of education, duration of symptoms, somatic symptom severity (PHQ-15), anxiety symptoms (HADS-A), depressive symptoms (HADS-D), number of comorbid physical diseases, time interval baseline – 2-months follow-up, time interval baseline – 4-months follow-up

* $p<0.05$

Appendix B. Results of mixed models analyses split up per group for effect modifiers: symptom duration and physical comorbidity

Primary outcome **RAND-36 PCS**	**Symptom duration below median (n=70-98)**		**Symptom duration above median (n=72-98)**		**Crude difference**			
	Intervention group (mean, sd)	**Control group (mean, sd)**	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Symptom duration below median**		**Symptom duration above median**	
Baseline	51.52 (9.80)	51.20 (10.05)	48.78 (9.97)	48.20 (9.57)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	52.08 (9.94)	49.95 (9.69)	48.88 (9.25)	48.52 (8.65)	n/a	n/a	n/a	n/a
4 months	54.90 (9.87)	50.74 (8.97)	47.41 (10.15)	46.00 (8.21)	n/a	n/a	n/a	n/a
12 months	54.13 (9.02)	48.63 (12.00)	48.01 (10.13)	47.42 (9.38)	n/a	n/a	n/a	n/a
Overall effect	n/a	n/a	n/a	n/a	3.83 (1.57 to 6.09)	0.001*	-0.18 (-2.40 to 2.03)	0.87
Secondary outcomes	**Symptom duration below median (n=70-98)**		**Symptom duration above median (n=72-98)**		**Crude difference**			
	Intervention group	**Control group (mean, sd)**	**Intervention group**	**Control group (mean, sd)**	**Symptom duration below median**		**Symptom duration above median**	

RAND-36 Bodily pain	**(mean, sd)**		**(mean, sd)**					
Baseline	48.35 (22.74)	45.51 (22.36)	43.92 (19.76)	45.56 (22.30)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	57.05 (23.05)	50.95 (26.21)	48.68 (19.58)	48.34 (22.81)	n/a	n/a	n/a	n/a
4 months	62.59 (19.86)	52.68 (22.67)	50.58 (21.77)	46.94 (21.03)	n/a	n/a	n/a	n/a
12 months	62.34 (18.00)	50.80 (27.53)	51.83 (21.44)	50.78 (24.86)	n/a	n/a	n/a	n/a
Overall effect	n/a	n/a	n/a	n/a	6.94 (1.05 to 12.84)	0.021*	0.68 (-5.41 to 6.78)	0.83
RAND -36 General health	**Symptom duration below median (n=70-98)**		**Symptom duration above median (n=72-98)**		**Crude difference**			
	Intervention group (mean, sd)	**Control group (mean, sd)**	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**Symptom duration below median**		**Symptom duration above median**	
Baseline	44.53 (17.67)	43.33 (18.00)	43.17 (17.88)	39.77 (14.74)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	46.36 (16.51)	40.69 (18.50)	42.68 (19.38)	45.45 (15.10)	n/a	n/a	n/a	n/a

4 months	49.64 (19.41)	47.90 (20.77)	43.69 (20.78)	47.04 (16.02)	n/a	n/a	n/a	n/a
12 months	53.10 (18.21)	45.00 (19.53)	22.87 (20.15)	48.09 (15.52	n/a	n/a	n/a	n/a
Overall effect	n/a	n/a	n/a	n/a	5.74 (0.96 to 10.52)	0.019*	-5.98 (-11.09 to -0.86)	0.022*
Primary outcome **RAND-36 PCS**	**0-2 comorbid physical diseases (n=69-91)**		**3 or more comorbid physical diseases (n=75-106)**		**Crude difference**			
	Intervention group (mean, sd)	**Control group (mean, sd)**	**Intervention group (mean, sd)**	**Control group (mean, sd)**	**0-2 comorbid physical diseases**		**3 or more comorbid physical diseases**	
Baseline	53.64 (9.38)	55.07 (8.78)	53.64 (9.38)	55.07 (8.78)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	53.65 (8.48)	52.85 (8.20)	53.65 (8.48)	52.85 (8.20)	n/a	n/a	n/a	n/a
4 months	55.24 (9.63)	51.47 (8.51)	55.24 (9.63)	51.47 (8.51)	n/a	n/a	n/a	n/a
12 months	55.38 (8.20)	50.85 (10.21)	55.38 (8.20)	50.85 (10.21)	n/a	n/a	n/a	n/a
Overall effect	n/a	n/a	n/a	n/a	3.55 (1.13 to 5.97)	0.004*	-0.02 (2.09 to 2.05)	0.99

Secondary outcome RAND-36 General health	0-2 comorbid physical diseases (n=69-91)		3 or more comorbid physical diseases (n=75-106)		Crude difference			
	Intervention group (mean, sd)	Control group (mean, sd)	Intervention group (mean, sd)	Control group (mean, sd)	0-2 comorbid physical diseases		3 or more comorbid physical diseases	
Baseline	49.01 (16.64)	46.41 (14.49)	49.01 (16.64)	46.41 (14.49)	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**
2 months	49.39 (17.25)	46.21 (16.18)	49.39 (17.25)	46.21 (16.18)	n/a	n/a	n/a	n/a
4 months	54.97 (19.96)	53.50 (16.20)	54.97 (19.96)	53.50 (16.20)	n/a	n/a	n/a	n/a
12 months	55.49 (18.57)	49.31 (15.91)	55.49 (18.57)	49.31 (15.91)	n/a	n/a	n/a	n/a
Overall effect	n/a	n/a	n/a	n/a	2.38 (-2.60 to 7.36)	0.35	-3.09 (-8.16 to 1.98)	0.23

Abbreviations: 95%CI: 95% Confidence Interval; n/a: not applicable; PCS: Physical Component Summary Score; sd: standard deviation

* $p<0.05$

Appendix C. Results of the mixed models per protocol analyses with the group of intervention patients who attended all 6 sessions with the MHNP

	Crude analyses		Adjusted analyses [a]	
	B (95% CI)	**p-value**	**B (95% CI)**	**p-value**
Primary outcome				
RAND-36 PCS	2.23 (0.39 to 4.08)	0.018*	2.20 (0.26 to 4.14)	0.026*
Secondary outcomes				
RAND-36				
MCS	-0.44 (-2.64 to 1.76)	0.70	-0.52 (-2.63 to 1.600)	0.63
Physical functioning	2.21 (-2.01 to 6.43)	0.30	2.54 (-1.68 to 6.76)	0.24
Role functioning/physical	7.87 (-1.72 to 17.47)	0.11	9.60 (-0.31 to 19.51)	0.058
Role functioning/emotional	-0.03 (-10.95 to 10.90)	1.00	0.29 (-10.62 to 11.20)	0.96
Social functioning	3.10 (-3.04 to 9.24)	0.32	1.88 (-4.27 to 8.04)	0.55
Bodily pain	4.29 (-0.53 to 9.11)	0.081	4.29 (-0.53 to 9.11)	0.081
Emotional well-being	-1.09 (-4.79 to 2.61)	0.56	-0.80 (4.44 to 2.85)	0.67
Energy/fatigue	3.03 (-0.60 to 6.65)	0.10	2.00 (-1.52 to 5.51)	0.27
General health	1.15 (-3.13 to 5.42)	0.60	0.15 (-4.46 to 4.75)	0.95
Anxiety symptoms (HADS-A)	0.19 (-0.53 to 0.91)	0.60	0.36 (-0.32 to 1.04)	0.30
Depressive symptoms (HADS-D)	-0.23 (-0.95 to 0.49)	0.53	-0.21 (-0.96 to 0.53)	0.58

Somatic symptom severity (PHQ-15)	-0.92 (-1.95 to 0.11)	0.080	-0.54 (-1.51 to 0.43)	0.28

Abbreviations: 95%CI: 95% Confidence Interval; HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale; MCS: Mental Component Summary Score; MHNP: mental health nurse practitioner; PCS: Physical Component Summary Score; PHQ-15: Patient Health Questionnaire 15-item somatic symptom severity scale

[a] adjusted for (if necessary): gender, age, level of education, duration of symptoms, somatic symptom severity (PHQ-15), anxiety symptoms (HADS-A), depressive symptoms (HADS-D), number of comorbid physical diseases, time interval baseline – 2-months follow-up, time interval baseline – 4-months follow-up

* $p < 0.05$

Appendix D. Results of the mixed models per protocol analyses with the group of intervention patients who attended all 6 or less sessions with the MHNP because their goals were achieved before the 6th session

	Crude analyses		Adjusted analyses [a]	
	B (95% CI)	**p-value**	**B (95% CI)**	**p-value**
Primary outcome				
RAND-36 PCS	2.16 (0.37 to 3.96)	0.018*	2.09 (0.24 to 3.94)	0.027*
Secondary outcomes				
RAND-36				
MCS	0.05 (-2.10 to 2.21)	0.96	-0.25 (-2.34 to 1.84)	0.81
Physical functioning	1.98 (-2.13 to 6.09)	0.35	1.71 (-2.38 to 5.80)	0.41
Role functioning/physical	8.70 (-0.62 to 18.03)	0.067	9.99 (0.30-19.68)	0.043*
Role functioning/emotional	1.22 (-9.35 to 11.79)	0.82	1.19 (-9.18 to 11.55)	0.82
Social functioning	4.14 (-1.85 to 10.12)	0.18	2.55 (-3.46 to 8.56)	0.41
Bodily pain	4.37 (-0.27 to 9.02)	0.065	3.85 (-0.65 to 8.36)	0.093
Emotional well-being	-0.45 (-4.07 to 3.17)	0.81	-0.57 (-4.16 to 3.01)	0.76
Energy/fatigue	3.97 (0.39 to 7.54)	0.030*	2.66 (-0.84 to 6.15	0.14
General health	1.15 (-2.99 to 5.29)	0.59	0.08 (-4.41 to 4.56)	0.97
Anxiety symptoms (HADS-A)	0.10 (-0.59 to 0.80)	0.77	0.38 (-0.30 to 1.05)	0.27

Depressive symptoms (HADS-D)	-0.31 (-1.00 to 0.39)	0.39	-0.23 (-0.99 to 0.52)	0.54
Somatic symptom severity (PHQ-15)	-1.04 (-2.03 to -0.04)	0.041*	-0.58 (-1.52 to 0.36)	0.23

Abbreviations: 95%CI: 95% Confidence Interval; HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale; MCS: Mental Component Summary Score; MHNP: mental health nurse practitioner; PCS: Physical Component Summary Score; PHQ-15: Patient Health Questionnaire 15-item somatic symptom severity scale

[a] adjusted for (if necessary): gender, age, level of education, duration of symptoms, somatic symptom severity (PHQ-15), anxiety symptoms (HADS-A), depressive symptoms (HADS-D), number of comorbid physical diseases, time interval baseline – 2-months follow-up, time interval baseline – 4-months follow-up

* $p < 0.05$

Appendix E. Results of the mixed models per protocol analyses with the group of intervention patients who attended at least 4 of the 6 sessions with the MHNP

	Crude analyses		Adjusted analyses [a]	
	B (95% CI)	**p-value**	**B (95% CI)**	**p-value**
Primary outcome				
RAND-36 PCS	2.25 (0.52 to 3.98)	0.011*	2.34 (0.55 to 4.14)	0.011*
Secondary outcomes				
RAND-36				
MCS	-0.09 (-2.14 to 1.97)	0.93	-0.55 (-2.59 to 1.50)	0.60
Physical functioning	2.04 (-1.78 to 5.86)	0.30	2.10 (-1.82 to 6.01)	0.29
Role functioning/physical	8.57 (-0.32 to 17.47)	0.059	9.51 (-0.35 to 18.66)	0.042*
Role functioning/emotional	0.55 (-9.61 to 10.71)	0.92	-0.23 (-10.65 to 10.18)	0.97
Social functioning	3.65 (-2.18 to 9.49)	0.22	1.17 (-4.63 to 6.98)	0.69
Bodily pain	4.82 (0.23 to 9.41)	0.040*	4.82 (0.23 to 9.41)	0.040*
Emotional well-being	-0.32 (-3.68 to 3.05)	0.85	-0.63 (-4.03 to 2.76)	0.72
Energy/fatigue	3.38 (-0.07 to 6.84)	0.055	1.88 (-1.46 to 5.22)	0.27
General health	0.86 (-3.02 to 4.74)	0.67	0.47 (-3.53 to 4.47)	0.82
Anxiety symptoms (HADS-A)	0.08 (-0.58 to 0.73)	0.82	0.42 (-0.22 to 1.06)	0.20
Depressive symptoms (HADS-D)	-0.20 (-0.86 to 0.45)	0.54	-0.16 (0.89 to 0.56)	0.66

Somatic symptom severity (PHQ-15)	-0.87 (-1.82 to 0.09)	0.074	-0.54 (-1.45 to 0.38)	0.25

Abbreviations: 95%CI: 95% Confidence Interval; HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale; MCS: Mental Component Summary Score; MHNP: mental health nurse practitioner; PCS: Physical Component Summary Score; PHQ-15: Patient Health Questionnaire 15-item somatic symptom severity scale

[a] adjusted for (if necessary): gender, age, level of education, duration of symptoms, somatic symptom severity (PHQ-15), anxiety symptoms (HADS-A), depressive symptoms (HADS-D), number of comorbid physical diseases, time interval baseline – 2-months follow-up, time interval baseline – 4-months follow-up

* $p < 0.05$